Executive function deficits mediate the association between very preterm birth and behavioral problems at school-age

Schnider, Barbara ; Disselhoff, Vera ; Held, Ulrike ; Latal, Beatrice ; Hagmann, Cornelia F ; Wehrle, Flavia M

Abstract: Background aims Children and adolescents born very preterm are at increased risk to develop executive function deficits and to suffer from social, emotional and attentional problems. This study investigated whether executive function deficits contribute to behavioral problems in children and adolescents born very preterm at school-age. Study design Thirty-eight children and adolescents born very preterm and 41 age-matched term-born peers were assessed at a mean age of 12.9 (±1.8) years with a comprehensive battery of executive function tests, including working memory, planning, cognitive flexibility, and verbal fluency. A composite score was calculated to reflect overall executive function abilities. To assess behavioral problems, parents completed the Strengths and Difficulties Questionnaire (SDQ). Mediation analysis was applied to quantify the effect of preterm birth on behavioral problems with executive function abilities as a mediating variable. Results Executive function abilities were poorer in the very preterm compared to the term-born group (d = 0.62, p = .005) and the parents of very preterm children reported more behavioral problems on the SDQ Total Difficulties Score (d = 0.54, p = .01). The effect of birth status on behavioral problems was significantly mediated by executive function abilities while adjusting for age at assessment, sex, and socioeconomic status ($F(2, 76) = 6.42$, p = .002, $R2 = 0.14$). Conclusion Results from this study suggest that the increase in behavioral symptoms in very preterm children at school-age compared to term-born peers may partly be explained by their executive function deficits. These findings highlight the importance of continuously monitoring the development of children born very preterm to provide optimal care as they grow up.

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Executive function deficits mediate the association between very preterm birth and behavioral problems at school-age

Barbara Schnider[a,b,1], Vera Disselhoff[a,b,1], Ulrike Held[c], Beatrice Latal[b,d], Cornelia F. Hagmann[a,b], Flavia M. Wehrle[a,b,d,*]

[a] University Children's Hospital Zurich, Department of Neonatology and Pediatric Intensive Care, Zurich, Switzerland
[b] University Children's Hospital Zurich, Children's Research Center, Zurich, Switzerland
[c] University of Zurich, Epidemiology, Biostatistics and Prevention Institute, Zurich, Switzerland
[d] Child Development Center, University Children's Hospital Zurich, Switzerland

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ABSTRACT

Background & aims: Children and adolescents born very preterm are at increased risk to develop executive function deficits and to suffer from social, emotional and attentional problems. This study investigated whether executive function deficits contribute to behavioral problems in children and adolescents born very preterm at school-age.

Study design: Thirty-eight children and adolescents born very preterm and 41 age-matched term-born peers were assessed at a mean age of 12.9 (±1.8) years with a comprehensive battery of executive function tests, including working memory, planning, cognitive flexibility, and verbal fluency. A composite score was calculated to reflect overall executive function abilities. To assess behavioral problems, parents completed the Strengths and Difficulties Questionnaire (SDQ). Mediation analysis was applied to quantify the effect of preterm birth on behavioral problems with executive function abilities as a mediating variable.

Results: Executive function abilities were poorer in the very preterm compared to the term-born group ($d = 0.62$, $p = .005$) and the parents of very preterm children reported more behavioral problems on the SDQ Total Difficulties Score ($d = 0.54$, $p = .01$). The effect of birth status on behavioral problems was significantly mediated by executive function abilities while adjusting for age at assessment, sex, and socioeconomic status ($F(2, 76) = 6.42$, $p = .002$, $R^2 = 0.14$).

Conclusion: Results from this study suggest that the increase in behavioral symptoms in very preterm children at school-age compared to term-born peers may partly be explained by their executive function deficits. These findings highlight the importance of continuously monitoring the development of children born very preterm to provide optimal care as they grow up.

1. Introduction

Very preterm birth is associated with an increased risk of developing behavioral problems in childhood and adolescence, even in the absence of major motor and cognitive impairments. Particularly, emotional, attentional and social difficulties, and internalizing symptoms are more prevalent in children born very preterm than in term-born peers [1]. These problems identified in early life have been shown to persist into adolescence [2,3] and young adulthood [4,5]. Importantly, behavioral problems often manifest in higher rates of subclinical psychiatric symptoms and an increased risk of psychiatric disorders in childhood and adult life, including attention deficit hyperactive disorder (ADHD), autism spectrum disorder, and anxiety [1,6,7].

In typically developing children, deficits in a set of higher-order cognitive functions needed for goal-oriented and adaptive behavior, termed executive functions [8,9], were found to play a significant role in explaining behavioral problems. For example, in a study with >4000 school-aged children, lower performance in tests of executive functions was found to be related to internalizing problems and stress reactivity [10]. Other studies further reported executive function problems in early childhood to predict both internalizing and externalizing symptoms [11–16].

Abbreviations: SDQ, Strengths and Difficulties Questionnaire; SES, socioeconomic status; ADHD, attention-deficit/hyperactivity disorder

* Corresponding author at: University Children's Hospital Zurich, Child Development Center, Steinwiesstrasse 75, 8032 Zurich, Switzerland.
E-mail address: flavia.wehrle@kispi.uzh.ch (F.M. Wehrle).

[1] Contributed equally as co-first authors.

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Executive functions are among the abilities most frequently found to be impaired in children and adolescents born very preterm [17–19]. Thus, their potential contribution to behavioral problems is of particular interest in this population. Previous research in this regard has largely focused on attentional problems: Findings consistently report poorer executive functions following very preterm birth to be related to higher rates of inattentive behavior [20,21] and higher scores on scales assessing symptoms of ADHD [22,23]. Recently, it has also been noted that executive function deficits in very preterm children co-occur with a variety of internalizing and externalizing behavioral problems, including symptoms of anxiety and depression, emotional reactivity, somatic complaints and aggression [24,25], however, these studies did not investigate a potential link between executive and behavioral problems. One other study identified a subtype of very preterm children with high behavioral problems and reported poorer working memory and inhibition abilities in this subtype compared to a subtype of very preterm children with low behavioral problems [26]. To date, only one study in preschoolers has investigated specifically whether executive function problems may explain the association between preterm birth and behavioral problems and, indeed, identified executive functions as a mediating factor [27]. As the demands placed on executive functions increase throughout school-age and potential deficits may only become apparent in highly demanding settings [28,29], it is important to investigate whether executive function problems contribute to the vulnerability to develop behavioral problems as very preterm children reach school age. Consequently, this study aims to do so.

2. Methods

2.1. Participants and study procedure

The inclusion and exclusion criteria of this study have been reported in detail previously [28]. In short, children and adolescents born very preterm, that is below 32 weeks of gestation, at the University Hospital Zurich, Switzerland were eligible for the study if they did not present a history of major neonatal brain injuries, had normal intellectual and motor abilities when assessed at the age of 5 years at a routine follow-up consultation, and were between the ages of 10 and 16 years at the time of the study. The data presented here were collected within the scope of a comprehensive study protocol, including a neurodevelopmental assessment, an overnight sleep EEG recording and cerebral MR imaging (see [30]). Of 175 children and adolescents eligible, 41 agreed to participate (23.4%). The participants' medical charts were obtained from the hospital archives and provided perinatal and routine follow-up data. We compared participants and non-participants. This analysis did not reveal group differences with regard to gestational age, birth weight, perinatal complications, and motor and intellectual abilities assessed at follow-up consultation at the age of 5 years. In addition, friends and siblings of very preterm participants and children and adolescents from local schools were recruited, resulting in a control group of 43 typically-developing, term-born and age-matched participants. Inclusion criteria for controls comprised birth at term ($\geq$37 weeks gestation), no perinatal complications and no neurodevelopmental illness as reported by the parents.

All study participants were examined at the Child Development Center at the University Children's Hospital Zurich between January and December 2013. The assessment took place over approximately 3 hours in the afternoon, either on weekdays or weekends, at the families' convenience. The study was approved by the local ethical committee. Parents of the study participants and participants older than 15 years signed a written consent form. Younger participants were asked for their oral consent. All participating children and adolescents were compensated with a gift voucher.

2.2. Instruments and measures

The neurodevelopmental assessment in this cohort has been detailed previously [28]. In summary, IQ was assessed with an abbreviated version of the German Wechsler Intelligence Scale for Children (WISC-IV, German version) [31,32] to estimate general cognitive abilities. To assess processing speed, the symbol search and coding subtests of the WISC-IV [31] were applied. Three subtests of the Cambridge Neuropsychological Test Automated Battery [33] were applied to assess core executive function abilities: Planning abilities were assessed with the Stockings of Cambridge task, working memory capacities were assessed with the Spatial Working Memory task, and cognitive flexibility was assessed with the Intra-/Extradimensional Shift task. Additionally, the participants' overall verbal fluency was assessed with four subtests of the Regensburger Wortflüssigkeitstest [34], of which the results were aggregated. The total score of each executive function task was z-transformed using the mean and standard deviation of the term-born group. This procedure provided equally scaled results for each of the four tasks. The z-scores were subsequently averaged and served as an overall estimate of the participants' executive function abilities, as previously shown in an overlapping cohort [35] and in a study assessing the association between executive functioning and behavior in preschoolers born preterm [27].

The German version of the Strengths and Difficulties Questionnaire (SDQ) [36] was used to screen for behavioral problems. The SDQ was designed as a brief rating instrument to assess behavior in children and adolescents between the ages of 4 and 16 years. Parents complete 25 items on their child's behavior over the past 6 months. The items are evenly distributed over five scales, of which four scales assess various symptoms related to Hyperactivity/Inattention, Conduct Problems, Emotional Symptoms and Peer Problems. Higher scores imply more behavioral problems (range per scale 0–10). A Total Difficulties Score is derived from the sum of the four symptom scales (range 0–40). An additional scale reports on the child's Prosocial Behavior with higher scores implying more frequent prosocial behaviors. Participants' SDQ scores were compared against those of a well-established German normative sample with specified cut-offs for all scales differentiating between ‘normal’, ‘borderline’ and ‘abnormal’ scores [37]. Five supplementary items in the questionnaire assess the level of general distress and the interference of the reported problems with the child's home and school life, friendships, and/or leisure activities. The sum of these items provides an Impact Score (ranging from 0 to 10) with scores $\geq$2 reflecting a ‘substantial impact’ [36]. In the current study, at least one parent was asked to complete the questionnaire. If answers from both parents were obtained (54%), the mothers' and fathers' scores on each item were averaged. Finally, an estimate of all study participants' socio-economic status (SES) was derived from parent-reported maternal education and paternal occupation using a six-point scale [38].

2.3. Statistical methods

Descriptive statistics included mean and standard deviation for the continuous variables and numbers and percentages of total for the categorical variables. Demographic and neurodevelopmental data was compared between groups using linear regression models adjusted for SES, independent samples *t*-test, Wilcoxon rank-sum test, or Chi-squared test, as appropriate. Normality of residuals was checked by visual inspection of QQ plots. Ninety-five percent confidence intervals (CI) are reported where relevant. Two-tailed *p*-values $<$ .05 were considered significant. Effect sizes were estimated by converting F-statistics to *d* (standardized mean difference between groups while taking into account SES [39]). Effect sizes of 0.2, 0.5, and 0.8 refer to small, medium, and large effects, respectively [40]. To investigate whether preterm birth exerts an effect on behavioral problems directly and/or indirectly through executive function abilities, mediation analysis as described by Hayes and Preacher [41] was applied. This

approach has been used previously in a study with preterm preschoolers [27]. A simple mediation model is defined as any causal system in which the effect of a given predictor (X) is suggested as influencing an outcome (Y) through an intervening variable, i.e., a mediator (M). The method assesses 1) the total effect (c) of X on Y without the mediator in the model, 2) the direct effect (c'), denoting the effect of X on Y while including the mediator, and, 3) the indirect effect (the product of path a [i.e., X to M] and b [i.e., M to Y]) through the mediator. In other words, the indirect effect is the difference between the total effect of X on Y and the direct effect of X on Y controlling for M (i.e., $a * b = c - c'$).

In our study, birth status (i.e. born very preterm vs. at term) was the predictor (X) for the Total Difficulties Score (Y) with the executive function composite score as potential mediator (M). To reduce bias introduced by potential confounders, the analyses were adjusted for age at assessment, sex, and SES. The indirect effect ($a * b$) and its uncertainty were obtained using a bootstrap of 10,000 resamples. We considered the effect to show evidence, if the 95% confidence interval did not include zero. Hayes and Preacher [41] propose the use of bootstrapping for quantification of indirect effects, which is particularly useful for smaller samples, since no assumptions of the sampling distribution need to be made. All statistical analyses were performed using *R* statistical software, Version 3.3.2 [42–46].

3. Results

3.1. Sample characteristics

The original group of very preterm participants included 41 children, whereas the age-matched control group comprised 43 children. For three very preterm and two term-born participants, questionnaire data were not available and they were excluded from further analyses. Therefore, the final sample included 38 very preterm and 41 term-born participants. Table 1 summarizes demographic and neurodevelopmental data of the participants. No group differences were found for age at assessment and sex. SES was higher in families of term-born participants. The estimated IQ was within the average range in all participants, with a lower mean in the very preterm than in the term-born group. The processing speed index did not differ between participants born very preterm and term-born peers.

3.2. Group differences in executive function performance and in SDQ scores

The mean executive function composite score was lower in the very preterm than in the term-born group ($d = 0.62$, 95% CI [0.19, 1.05]; Table 2).

In the very preterm group, on average, the Total Difficulties Score was 2.9 points higher ($d = 0.54$, 95% CI [0.11, 0.98]) than in the term-born group. On subscale level, more difficulties were observed in the domains Hyperactivity/Inattention and Emotional Problems in the very preterm compared to the term-born group. No group differences were apparent for the domains Conduct Problems, Peer Problems, and Prosocial Behavior (Table 2).

Among the 79 study participants, 6 children had scores outside the normal range on the Total Difficulties Score as defined by a German normative sample [37]. All of those participants were born very preterm. The impact of difficulties on home life, friendships, school, and/or leisure activities was higher in the very preterm than in the term-born group. Eight of the parents of children born very preterm reported a substantial impact (Impact Score of ≥ 2) [36], but none of the parents of term-born participants did. Fig. 1 shows the distribution of the participants in the two groups on the Total Difficulties Score (a) and on subscale level (b–f).

3.3. Mediation analyses

Fig. 2 shows the results of the mediation analysis. The total effect of birth status on the Total Difficulties Score was $c = 2.27$ (95% CI [0.37, 4.17], $p = .02$), while the direct effect of birth status on the Total Difficulties Score including the executive function composite score diminished to $c' = 1.51$ (95% CI [−0.45, 3.47], $p = .14$). The indirect effect for birth status on the Total Difficulties Score through the executive function composite score was $a * b = 0.79$, 95% CI [0. 17, 1.68]. The overall model, including the EF composite score and when adjusting for age at assessment, sex, and SES accounted for 14% of the variance on the Total Difficulties Score ($F(2, 76) = 6.42$, $p = .002$). Similar results were found if only mothers' ratings on the SDQ questionnaire (n = 71) were considered for the analyses (data not shown). Adding the processing speed index as a covariate to the model, did not change the model substantially ($p = .20$).

4. Discussion

In this study, we found more behavioral problems and poorer executive functions in children and adolescents born very preterm compared to their term-born peers. Further, our results suggest that the increase in behavioral symptoms in the very preterm group may partly be explained by their executive function deficits.

Previous studies have reported that deficits in working memory, inhibition and cognitive flexibility – some of the core executive abilities – are associated with inattentive and hyperactive behavior in children born very preterm [20–23]. Also, problems in executive functions were found to co-occur with behavioral problems in very preterm preschoolers [24,25] and to be more likely in a subtype of very preterm children with high behavioral problems compared to a subtype with low behavioral problems [26]. The current study complements these findings by reporting a set of executive functions to mediate, i.e., partly explain, the effect of very preterm birth on a range of behavioral problems, including symptoms of inattention/hyperactivity, emotional, and peer problems.

At preschool age, parent-rated executive function abilities were

Table 1
Descriptive statistics of the very preterm and the term-born group.

	preterm-born (n = 38)			term-born (n = 41)			p
Male (n, %)	21 (55.3)			20 (48.8)			.73
	M	SD	range	M	SD	range	
Gestational age (in weeks)	29.6	1.9	25.1-32.0			> 37	
Birthweight (in grams)	1271	336	840-1990			> 2500	
Age at assessment (in years)	12.7	1.6	10.4-16.6	13.1	2.1	10.0-16.9	.31
Socioeconomic status[a]	3.6	0.9	2-5	4.0	0.9	2-5	.05
Processing speed index	106.3	12.0	81-131	109.2	10.5	94-134	.26
IQ estimate	104.4	7.2	91.3-117.5	109.6	6.9	98.8-128.8	.002

M: mean; *SD*: standard deviation.
[a] Six-point scale (0-6); higher values reflect higher socioeconomic status.

Table 2
Executive function composite score and parent-rated SDQ scores in very preterm and term-born participants.

	preterm-born			term-born				
	n = 38			n = 41				
	M	SD	range	M	SD	range	d [95% CI]	p
EF composite score[a]		-0.6 (0.8)	[-2.5-0.6]		0.0 (0.8)	[-2.0-1.1]	0.62 [0.19, 1.05]	.005
Total Difficulties Score[b]		7.1 (5.4)	[0-26]		4.2 (3.2)	[0-12]	0.54 [0.11, 0.98]	.01
Hyperactivity/Inattention		2.7 (2.0)	[0-7.5]		1.5 (1.5)	[0-5.5]	0.49 [0.05, 0.95]	.01
Emotional Problems		1.6 (1.5)	[0-7]		0.8 (1.0)	[0-3]	0.56 [0.13, 0.99]	.02
Conduct Problems		1.6 (1.7)	[0-7]		1.2 (1.1)	[0-4]	0.23 [-0.21, 0.67]	.29
Peer Problems		1.3 (1.6)	[0-6]		0.7 (1.0)	[0-4.5]	0.42 [-0.01, 0.85]	.20
Prosocial Behavior		8.1 (1.5)	[10-5]		8.5 (1.3)	[10-4]	0.29 [-0.15, 0.73]	.18
Impact Score		0.9 (1.4)	[0-5]		0.1 (0.2)	[0-1]	0.62 [0.18, 1.06]	.002

EF: Executive function; SDQ: Strengths and Difficulties Questionnaire; *M*: mean; *SD*: standard deviation; *d*: Effect size estimates adjusted for SES with 95% Confidence Intervals; *p*: *p*-values adjusted for SES.

[a] Z-scores; lower values indicate worse performance.

[b] Higher scores indicate more problems, except for the Prosocial Scale (higher scores = more positive prosocial behavior).

found to mediate the association between gestational age and behavioral problems in children born very preterm [27]. Executive functions undergo rapid development across school-age [9,49] and it remains unclear whether very preterm children catch up to their term-born peers as they grow up [50–52]. Importantly, the current study demonstrates that executive function deficits continue to contribute to behavioral problems as very preterm individuals reach adolescence. These findings are particularly relevant as they stem from a cohort of individuals without any major neurodevelopmental deficits, thus, representing the majority of today's very preterm survivors [53].

In line with the current literature [17–19], in this study, executive function abilities of children and adolescents born very preterm were found to be impaired compared to typically-developing term-born peers. Recently, it has been reported that the rate of executive function deficits following very preterm birth has increased over the past three birth eras [47]. This highlights the importance of comprehensively investigating the potential consequences of these deficits for the long-term development of preterm survivors. Notably, executive function abilities have previously been suggested to rely on the integrity of other cognitive capacities such as processing speed (e.g., [54]). Further, processing speed and working memory have been found to mediate the negative impact of preterm birth on academic difficulties [55]. In the current study, processing speed did not alter the mediating effect of executive functions on the association between preterm birth and behavioral problems. Further studies are, however, needed to confirm this.

In children born very preterm, executive function deficits have been attributed to alterations in brain development due to preterm birth. For example, reduced cortical and subcortical brain volumes and impairments in cortico-cortical and subcortical-cortical connectivity were found to be related to poorer executive function performance in very preterm children and adolescents [56–61]. Interestingly, behavioral and psychiatric symptoms in very preterm children and adolescents have also been reported to be associated with brain alterations, particularly in networks including subcortical regions [62–64]. As brain networks supporting executive functions have been suggested to overlap with networks implicated in psychiatric disorders (e.g., [65]), potentially, shared neuronal correlates underlie both executive function deficits and behavioral problems in children and adolescents born very preterm. Studies including thorough assessments of cognitive and behavioral outcome alongside comprehensive neuroimaging are needed to investigate this further.

Significant group differences were found in the Total Difficulties Score, and on the Inattention/Hyperactivity and the Emotional Problems subscales of the SDQ. This is in line with previous research reporting behavioral difficulties in children and adolescents born very preterm and broadly corresponds to a proposed 'preterm behavioral phenotype' [1,48]. Behavioral difficulties early in life have been shown to predict later behavioral problems in children born very preterm [66–69], with problems persisting into adult life [4,70–72]. Further, behavioral difficulties have been reported to be associated with learning difficulties and academic underachievement [73], and to negatively impact various life domains (e.g., home life, friendships, school/work, leisure activities) [70,74]. In this study, behavioral difficulties of children and adolescents born very preterm were expressed as subclinical symptomatology, with few children and adolescents exceeding the clinical cut-off values provided by a normative sample [37]. This is consistent with a report of very preterm children which indicated subclinical symptoms even in a behavioral subtype characterized by high problems [26]. Strong evidence exists that even subclinical behavioral difficulties may serve as antecedents of later, more severe mental health issues in preterm cohorts [66–69]. Interestingly, in the current study, parents rated not only clinical but also subclinical behavioral difficulties as interfering with their child's home life, friendships, classroom learning, and leisure activities. Together, this highlights the importance of identifying even mild behavioral problems early to minimize their negative impact for the long-term development after very preterm birth.

Behavioral problems and psychopathology in childhood and adolescence have been reported to be more common in individuals who experienced infant regulatory problems, including excessive crying, sleeping and feeding problems (e.g., [75–77]). Infants born very preterm are at higher risk of early regulatory problems compared to term-born peers [78–80] and regulatory problems have been shown to predict behavioral symptoms in childhood and adolescence [81,82]. Interestingly, early regulatory functions were also predictive of executive function abilities at early school-age in very preterm children [81,83]. While a causal link needs to be addressed in future studies, it may be hypothesized that behavioral problems in childhood and adolescence emerge from early regulatory problems and subsequent executive function difficulties as very preterm children grow up.

4.1. Limitations

The sample size in the current study was relatively small, limiting statistical power. Increasing the number of participants was, however, not feasible as the data were collected within the scope of a comprehensive study protocol, including cerebral MR imaging and an overnight stay at the hospital for a sleep EEG. Potentially, the comprehensiveness of the study protocol lowered the follow-up rate and, thus, the generalizability of the results for the population of children and adolescents born very preterm may have been reduced. Along these lines,

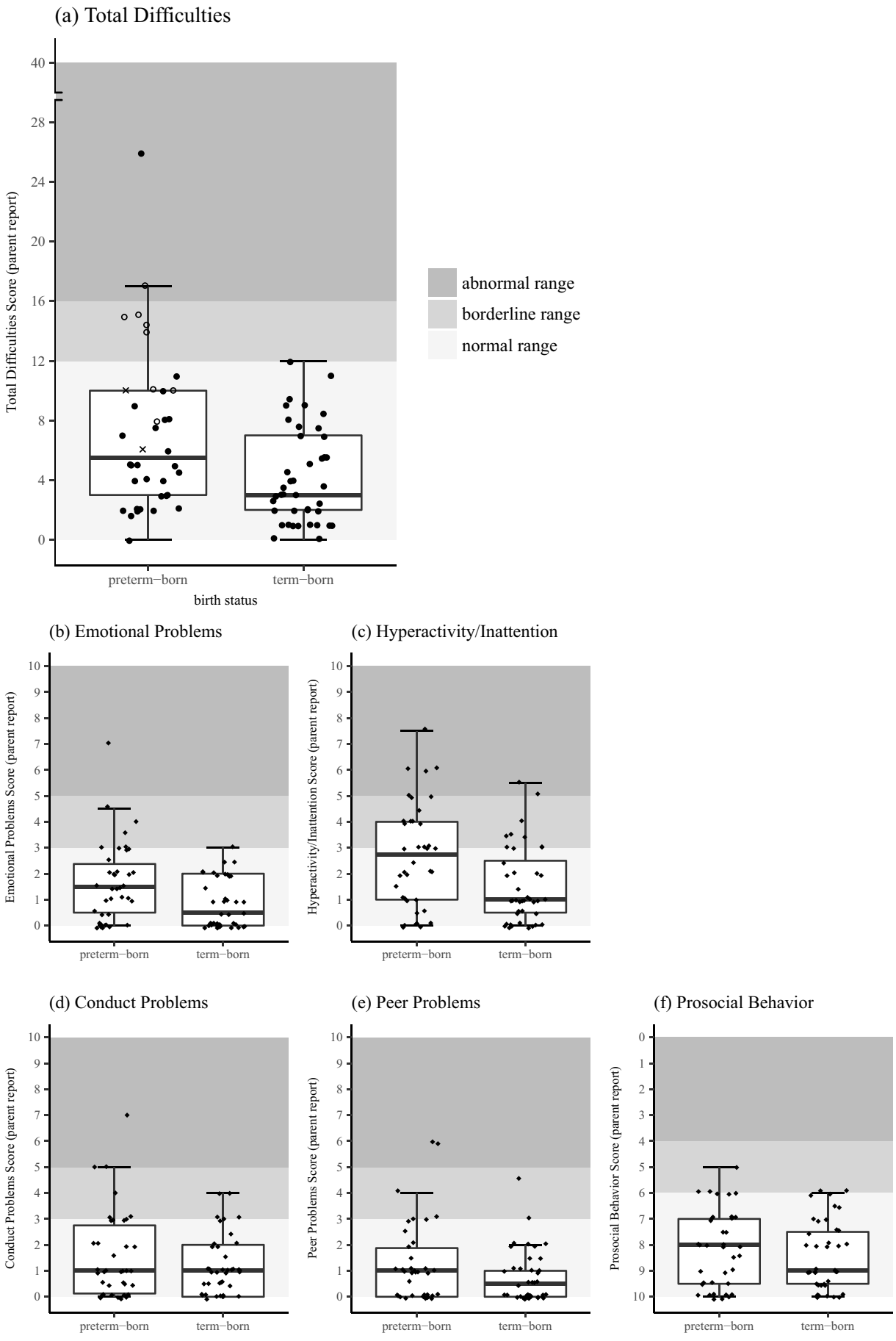

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Fig. 1. a. Distribution of the Total Difficulties Score in the very preterm and the term-born group. Additionally, the Impact Score is displayed. Filled dots represent participants with a low Impact Score (< 2), empty dots represent individuals with a high Impact Score (2–10), crosses represent individuals with no data available for the Impact Score.
b–f. Distribution of the SDQ subscale scores in the very preterm and the term-born group. Diamonds represent individual participants. The upper whisker is either the maximum score or the 3rd quartile plus 1.5 times the interquartile range (the length of the box). The lower whisker is either the minimum score or the 1st quartile minus 1.5 times the interquartile range. For illustrational purpose, individual data points are drawn with jitter ($X = 0.2$, $Y = 0.1$).

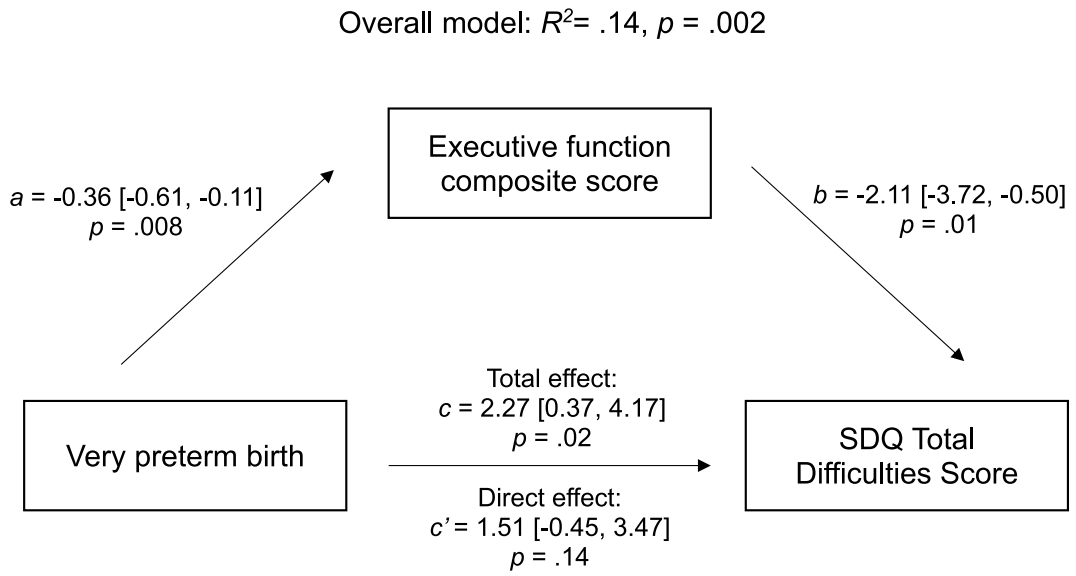

Fig. 2. Effect estimates from mediation analysis with 95% confidence intervals and *p*-values. The indirect effect of birth status (i.e. very preterm birth vs. at term) on the SDQ Total Difficulties Score through the executive function composite score was $a * b = 0.79$, $SD = 0.39$, 95% CI [0. 17, 1.68]. The effects of age at assessment, sex, and SES were adjusted for.

in the current study, the very preterm group did not present with an increased rate of peer and social problems as previously suggested for the preterm population (e.g., [5]). Possibly, the overnight stay in a sleep lab prevented those children and adolescents with particular problems in these areas from participating in the study. The very preterm group consisted of healthy, high-functioning individuals with normal general intellectual and motor abilities. This may have further limited the detection of potential differences between individuals born very preterm and at term. However, the observed differences and associations may therefore be robust and, thus, particularly relevant for a better understanding of what underlies behavioral problems following very preterm birth.

In this study, we report on cross sectional data. Studies in typically-developing children reported executive function problems in preschool age to predict later behavioral problems [11–16]. Similarly, longitudinal studies are needed to shed light on whether executive function deficits precede behavioral problems as children born very preterm grow up. Further, in our sample, the participants' age range was rather broad, varying from late childhood (i.e., 10 years) into adolescence (i.e., 16 years). This spans important periods of development in executive function abilities [84] as well as behavioral problems [85,86]. Importantly, the mediating effect of executive function abilities was apparent while adjusting for age at assessment and may, thus, occur independent of age.

Other factors than those considered in the current study (e.g., environmental factors such as early life stress and parental behavior) are likely to play a crucial role in the development of behavioral problems and mental health issues following preterm birth [87]. Their impact could not be investigated in the current study as they were not assessed. Similarly, in a large study with typically-developing children, the associations between neurocognitive measures and behavioral symptoms were consistent but small, suggesting additional factors contributing to the development of behavioral problems [10]. Future research in both typical and atypical development should, thus, consider such factors.

5. Conclusion

Results from this study suggest that poorer executive function abilities may partly explain the higher rate of behavioral problems in children and adolescents born very preterm than in their term-born peers. Since even subtle behavioral symptoms may develop into more severe mental health issues as children grow up, a continued follow-up of the development of very preterm individuals is crucial to ensure optimal development following very preterm birth.

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CRediT authorship contribution statement

Barbara Schnider: Conceptualization, Formal analysis, Writing - original draft. **Vera Disselhoff:** Conceptualization, Formal analysis, Writing - original draft. **Ulrike Held:** Conceptualization, Formal analysis, Writing - review & editing. **Beatrice Latal:** Conceptualization, Methodology, Writing - review & editing. **Cornelia F. Hagmann:** Conceptualization, Methodology, Investigation, Supervision, Funding acquisition, Writing - review & editing. **Flavia M. Wehrle:** Conceptualization, Methodology, Investigation, Supervision, Writing -

review & editing.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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